IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant(s):	*Turner et al.*	Group Art Unit:	1646
Application No.:	09/714,882	Examiner:	O'Hara, E.B.
Filed:	November 16, 2000		
Title:	Human *Notch* Ligand Proteins and Polynucleotides Encoding the Same	Atty. Docket No.	LEX-0091-USA

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed December 3, 2003. The Notice of Appeal was timely submitted on March 3, 2003, and was received in the Patent and Trademark Office ("the Office") on March 7, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of five months to and including October 7, 2003 and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(2) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief (**$160.00**), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on November 16, 2000, claiming the benefit of U.S. Provisional Application Number 60/165,959, which was filed on November 17, 1999, and included original claims 1-6. A restriction and Election Requirement was issued on January 30, 2002, in which the Examiner determined that the original claims were directed at four separate and distinct inventions. In a Response to the Restriction and Election Requirement, submitted on February 27, 2002, Applicants elected with traverse to prosecute the claims of Group 1(claims 1 and 2).

A First Official Action, was issued on June 13, 2002 ("the First Action"), in which as the result of Applicant's traversal, claims 1-6 were accepted for examination. Claims 1-6 were then rejected under 35 U.S.C. § 101, as allegedly lacking patentable utility and under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, Claims 1 and 2 were also rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In a response to the First Official Action, submitted to the Office on September 10, 2002 ("response to the First Action"), Appellants amended claims 1-2 to further improve their clarity, adde new claims 7 and 8 and respectfully traversed the rejections of claim 1-6 under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph, as well as the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph.

A Second and Final Official Action, was issued on December 3, 2002 (the "Final Action"), in which rejection of claims 1-8 was maintained under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph, as one skilled in the art clearly would not know how to make or use the invention. In a response to the Final Action, submitted on May 5, 2002 ("response to the Final Action"), Appellants responded to the rejection of claims 1-8 under 35 U.S.C. §§ 101 and 112. Applicants filed a notice of Appeal on March 3, 2003. An Advisory Action ("the Advisory Action") was mailed on August 12, 2003, in which the rejection of claims 1-8 under 35 U.S.C. §§ 101 and 112 was maintained. Therefore, claims 1-8 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

For the purposes of Appeal Appellants believe that no additional outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human sequences that encode a novel human *Notch* ligand protein similar to SEL1L(Sel-1suppressor of lin-12, *C. elegans*)-like). Also disclosed is the tissue specific expression pattern of these sequences in human testis cells only (Page 3, lines 11-12) and naturally occurring polymorphisms that exist within these molecules (page 14, lines 6-11). The specification details a number of uses for the presently claimed sequences, including the detection and diagnosis of human diseases such as, *inter alia*, diabetes, heart disease and cancer. Additional uses for the sequences of the present invention include assessing temporal and tissue specific gene expression patterns (specification at page 5, line 17), particularly using a high throughput "chip" format (specification at page 5 through page 6), mapping the sequences to a specific region of a human chromosome and identifying protein encoding regions (specification at page 8, line 12-18), determining the genomic structure (specification at page 8, line 6-12), and in diagnostic assays such as forensic analysis, human population biology and paternity determinations (see, for example, the specification at page 8 line 12 and page 14, line 30) wherein the sequences of the present invention are particularly useful as the specification identified polymorphisms (page 14, lines 6-11) that can be used in these assays. Thus, Appellants have described novel nucleic and amino acid sequences, their tissue specific expression in testis and naturally occurring polymorphisms (page 14, lines 6-11) that exist within the sequences of the present invention.

VI. ISSUES ON APPEAL

1. Do claims 1-8 lack a patentable utility?
2. Are claims 1-8 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-8 Lack a Patentable Utility?

The Final Action rejected and the Advisory Action maintained the rejection of claims 1-8 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility, this rejection is maintained in the Advisory Action.

Appellants have described a novel human *Notch* ligand nucleic and amino acid sequences, their testis specific expression pattern and naturally occurring polymorphisms (page 14, lines 6-11) that exist within the sequences of the present invention.

First, as set forth in the response to the First Action and the response to the Final Action, Appellants would like to invite the Board's attention to the fact that a sequence that is 99.8% identity over the 506 amino acid overlap to a described sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Appellants* as a Novel Protein similar to SEL1L (Sel-1suppressor of lin-12, *C. elegans*)-like) (GenBank accession number: Q9UGD3, alignment and GenBank report provided in **Exhibit A**). SEL1L is a well established *Notch* ligand. Given this clear evidence that those skilled in the art have independently identified the sequences of the present invention as encoding a protein similar to SEL1L a well-established *Notch* ligand, there can be no question that Appellants' asserted utility for the described sequences is "credible." As such, the scientific evidence of identity at both the amino acid and nucleic acid levels clearly establishes that those of skill in the art would recognize the sequences of the present invention as a human *Notch* Ligand , a class of proteins with well known

function. Therefore, Appellants have described a utility in full compliance with the provisions of 35 U.S.C. section 101, and the Examiner's rejection should be overturned.

The biological significance and function of *Notch* signaling pathway and *Notch* ligands is supported by many scientific publications, among others, the two review articles that were cited by the Advisory Action, which clearly support Applicant's assertions made in the specification (page 14 lines 12-23) that "Because of the diverse activities that have been associated with *Notch* signaling pathways, *Notch* receptors, and their associated ligands and antagonists have been subject to intense scientific scrutiny. For examples of how the described NHPs, or related *Notch* receptors can be produced, antagonized, used, processed, applied, and delivered, see, for example, U.S. Patent Nos. 5,786,158 and 5,780,300, and 5,856,441 the disclosures of which are hereby incorporated by reference in their entirety. Given their structural relatedness to *Notch* ligands, the described NHPs are suitable for use and modification as contemplated for other *Notch* ligands and antagonists." Also in the specification in Section 2 Applicants taught that "SEL-1 proteins are negative regulators of *Notch* family receptors. *Notch* receptors and their associated signaling pathways have been associated with development, apoptosis, neuron growth and maintenance. Genetic alterations in *Notch* receptors and their ligands have been associated with multiple human processes and disorders such as diabetes, cancer (*inter alia* pancreatic cancer and insulinomas), stroke, Alzheimer's and other neurodegenerative diseases, cholesterol and fat metabolism (HMG CoA reductase degradation), blood pressure abnormalities, Coronary artery disease and immunity (Donoviel and Bernstein, PCT application, publication No. WO99/27088, which is incorporated herein by reference in its entirety)." The utility of *Notch* proteins and ligands are therefore clearly well-known to those of skill in the art.

The Advisory Action maintains the position taken in the Final Action, that function can not be reliably predicted based on structural similarity and reiterates the citation of Yan et al. ("Yan"; 2000, Science 290:523-527) for the proposition that a protein's membership in a particular family does not nessicarily predict a function (Action at page 4 line 4). However, this paper cites only <u>one</u> example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). While it is true that in this

specific case this amino acid change results in binding to different receptors, it is important to note, however, that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan is hardly indicative of a high level of uncertainty in assigning function based on sequence or family membership, and thus does not support the alleged lack of utility. The action also cites a series of older articles each of which is said to support the proposition that function cannot be predicted based on structural information. It should be noted that none of these articles refer to *Notch* ligands. Applicants respectfully disagree and believe that those of skill in the art recognize the structure-function relationship and that this position is supported by the many references often provided by Examiners as teaching that structural homology alone is not a good predictor of function. See, for example, Ji *et al.* ("Ji":1998, J. Biol. Chem. *273*:17299-17302). Ji notes that "a substantial degree of amino acid homology is found between members of a particular subfamily" (Ji at 17299, first paragraph). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that family and supports applicants assertion that a structure-function relationship is well- established.

Furthermore, these articles are just examples of the few spurious articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. Appellants agree that there is not 100% consensus within the scientific community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants respectfully point out that the lack of 100% consensus on prediction of protein function from homology information is irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is **not the standard** for patentability under 35 U.S.C. § 101. Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those

skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools, as evidenced by extensive number of journal articles (which support Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatic predictions), and would thus **believe** that Appellants sequence is a CUB domain containing protein. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus or 100% accuracy, Appellants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

While not reiterated in the Advisory Action the Examiner earlier included as a reason for the alleged lack of utility of the present invention is the concern that the present application contained no working examples of any kind, only assertions. This emphasis is misplaced as it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Applicants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility.

The Advisory Action maintains that Appellants' assertions regarding the use of the presently claimed polynucleotides on DNA gene chips, based on the position that such a use would allegedly be generic and therefore does not represent specific utility. Further, these Actions seem to be requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Appellants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Appellants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications.

However, clearly given the extensive utility described above for the molecules encoded by the sequences of the present invention and evidence that the claimed sequences provide a specific marker of the gene encoding a testis specific *Notch* ligand rovides a unique identifier of the corresponding gene in the human genome. Such specific markers are targets for discovering drugs that are associated with human disorders and diseases such as, *inter alia*,diabetes, heart disease and cancer (specification page 3, lines 2-3). Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 5, line 30 through page 6, line 33. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit B**), 5,556,752 (**Exhibit C**), 5,744,305 (**Exhibit D**), as well as more recently issued U.S. Patent Nos. 5,837,832 (**Exhibit E**), 6,156,501 (**Exhibit F**) and 6,261,776 (**Exhibit G**).

The Board is further requested to consider that, given the huge expense of the drug discovery process, even negative information has great "real world" practical utility. Knowing that a given gene is not expressed in medically relevant tissue provides an informative finding of great value to industry by allowing for the more efficient deployment of expensive drug discovery resources. Such practical considerations are equally applicable to the scientific community in general, in that time and resources

are not wasted chasing what are essentially scientific dead-ends (from the perspective of medical relevance). Clearly, compositions that enhance the utility of such DNA gene chips, such as the presently claimed sequences encoding a testis specific *Notch* ligand, must in themselves be useful. Moreover, the presently described protein (*Notch* ligand) provides uniquely specific sequence resources for identifying and quantifying full length transcripts that were encoded by the corresponding human genomic locus. Accordingly, there can be no question that the described sequences provide an exquisitely specific utility for analyzing gene expression.

The utility of the sequences of the present invention are further enhanced by the description in the specification of the testis specific expression of the sequences of the present invention (page 3, lines 11-12) and the description of polymorphisms (page 14, lines 6-11). These teachings along with the above evidence that the molecules of the present invention encode a protein of known function and that Appellants have used methods described in the specification as filed to biologically validate their assertions that the sequence of the present invention have utility as drug targets for human disease, clearly demonstrate outstanding utility of the sequences in DNA chip expression analysis.

Still further, as only a small percentage of the genome (2-4%) actually encodes exons, which in turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications. This further discounts the Examiner's position that such uses are "generic". The present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Additional evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-

Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit H**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit I**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

As a still further example of utility is the use of the present sequences in such diagnostic assays (for example, the specification at page 8 line 12 and page 14, line 30) as those associated with identification of paternity and forensic analysis, among others. The sequences of the present invention have particular utility as the application as filed identified several polymorphisms (page 14, lines 6-11). This is also not a case of a potential utility. Appellants respectfully submit that even in the worst case scenario, the described polymorphisms are each useful to distinguish 50% of the population (in other words, the marker being present in half of the population) and that the ability of a polymorphic marker to distinguish at least 50% of the population is an inherent feature of any polymorphic marker, and this feature is well understood by those of skill in the art. Appellants note that as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Appellants support for Appellants' assertion of utility is provided by the fact that the skilled artisan would readily recognize and easily believe that the presently described polymorphic markers could be useful in forensic analysis. The fact that forensic biologists use polymorphic markers

such as those described by Appellants every day provides more that ample support for the assertion that forensic biologists would also be able to use the specific polymorphic markers described by Appellants in the same fashion. Therefore, again it is clear that the sequences of the present invention have utility.

Given the physiologic activity and importance of *Notch* ligands as known to those of skill in the art, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins, particularly due to the established role of *Notch* ligands in human disorders, such as but not limited to diabetes, heart disease and cancer (specification at page 3, lines 2-3). The use of the claimed polypeptide in an array for screening purposes Appellants respectfully point out that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as have tissues of interest, as in the present case. Once the role of the particular nucleic acid is known, the level of gene expression has and even greater significance. By identifying the physiological activity role of the claimed sequence, the claimed sequence has a far greater utility in gene chip applications that just any random piece of DNA. Appellants respectfully submit that **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, is distinct from the requirement for a **unique** utility, which is clearly an improper standard. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991; "*Carl Zeiss*"):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Therefore, just because other nucleic acid sequences find utility in gene chip applications does not mean that the use of Appellants' sequence in gene chip applications is not a specific utility. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no

longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the specific utility the present nucleotide sequence has in determining the genomic structure of the corresponding human chromosome (specification at page 8, line 6-12), for example mapping the protein encoding regions as described in the specification (page 8, line 12-18) and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequence. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the

significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* defines that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence supporting the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit J**. This is the result of a blast analysis using SEQ ID NO:1 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 20 exons spread non-contiguously along a region of human chromosome 20, at approximately 20p12, which are contained within partially overlapping BAC clones, AL109657.8 and AL117333.26. Thus clearly one would not simply be able to identify the 20 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

The question of utility is a straightforward one. As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, with regards to the issue of due process, while Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of

35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit K**), 5,654,173 (**Exhibit L**), and 5,552,281 (**Exhibit M**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit N**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Given the rapid pace of development in the biotechnology arts, it is difficult for the Appellants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Appellants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

Thus in summary, Appellants have described novel nucleic and amino acid sequences, their tissue specific expression and naturally occurring polymorphisms that exist within these molecules. Furthermore, the sequences of the present invention encode a human *Notch* ligand protein, a protein class with well recognized utility. Therefore, given the broad utility described for the sequences of the

present invention, Appellants respectfully submit that the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

B. Are Claims 1-8 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-8 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in **Section VIII(A)** concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana*, *supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-5 have been shown to have "a specific, substantial, and credible utility", as detailed in **Section VIII(A)** above, the present rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. An isolated nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.

5. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:8.

6. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:10.

7. An expression vector comprising a nucleic acid sequence of Claim 2.

8. A cell comprising the expression vector of Claim 7.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-8 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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